

EXHIBIT 10



BREAST IMPLANT-ASSOCIATED ANAPLASTIC LARGE CELL LYMPHOMAS

AN EXPERTS OPINION

The French National Cancer Institute

PREAMBLE

A first case of breast implant-associated anaplastic large cell lymphoma (BIA-ALCL) was diagnosed in France in 2011. Specific surveillance was organized by the French Medicine Agency (ANSM), in association with the French national network of experts LYMPHOPATH, which is in charge of organising a confirmatory anatomopathological examination and recording the new cases of lymphoma. In the context of the monitoring programme set up, the French health authorities analyse the ALCL cases reported each year.

Following the notification of new cases of BIA-ALCL to ANSM, the French General Directorate of Health asked the French National Cancer Institute (INCa) to form a group of experts in order to "(i) analyse all the cases referred by ANSM; (ii) analyse the data from the LYMPHOPATH network and any other available data in order to look for any other ALCL cases; (iii) determine the prevalence and incidence of breast ALCL in women with breast implants, taking international data into account as far as possible; (iv) to elaborate the management of women diagnosed with BIA- ALCL, and for women with breast implants in general regarding this signal."

INCa EXPERTS OPINION

The present experts opinion was issued at a single plenary meeting held on 4 March 2015. The opinion reports the points of consensus between experts.

Given the rarity of this disease and the limited data available, the present opinion will have to be updated as new knowledge will be acquired on breast implant-associated anaplastic large cell lymphomas. The interest of sharing information on this disease at European or even global level is emphasised.

This opinion does not make any recommendations on conducting research projects. A specific reflection is underway within INCa on this subject.

ANALYSIS OF CASES OF BREAST IMPLANT-ASSOCIATED ANAPLASTIC LARGE CELL LYMPHOMAS

Based on data from the literature and the 18 French cases reported to ANSM and recorded in LYMPHOPATH, the group of experts have selected the term "breast implant-associated anaplastic large cell lymphoma" (BIA-ALCL). The expert group believes that it is a specific entity, and that it should be incorporated into the WHO classification at its next revision, under the term "BIA-ALCL."

There seem to be two forms, a localised form confined to the capsule, and an infiltrating form (with a mass adjacent to the periprosthetic capsule). At the time of diagnosis, spread is generally confined to the periprosthetic capsule. In a few cases, however, the BIA-ALCL extends beyond the capsule (stage IIE-IV).

Immunohistochemical characterisation reveals constant expression of CD30 by the tumour cells, a T cytotoxic phenotype and, in almost all reported cases, an absence of ALK expression.

In France, a confirmatory anatomopathological examination of all lymphoma cases has been implemented via the LYMPHOPATH national network of experts. Diagnosis of BIA-ALCL is indeed complex, and confirmatory examination has allowed it to be established both histologically and phenotypically in a number of cases.

Data from the literature are in agreement with data inherent to the French cases in terms of clinical characteristics of patients and characteristics of breast implants. BIA-ALCL occurs on average between 11 and 15 years after insertion of the first implant. However, there can be wide variations in the length of this period (2-37 years). This disease may occur in women fitted with a breast implant for either cosmetic purposes or as part of breast reconstruction following breast cancer. The majority of women were found to have a macrotextured implant at a given moment of their history. This disease is most often manifested as a periprosthetic effusion (seroma).

Short-term survival seems good for patients without mass at diagnosis, but long-term survival cannot be estimated, given the short follow-up, for both data from the literature and French cases. According to data from the literature, short-term survival seems less good for patients with a mass at diagnosis. An extensive form (II-IV) also seems to be a poor prognostic factor.

ESTIMATION OF THE RISK OF OCCURRENCE OF BIA-ALCL

There is a clearly established link between the occurrence of this disease and the presence of a breast implant. The group emphasises that the frequency of this complication is, however, very low.

Due to the difficulty of determining the number of women with breast implants, and the potential under-notification of BIA-ALCL cases, estimation of the risk of its occurrence can be only very approximate. By accepting a large number of assumptions, an estimate of the cumulative incidence over a period of 6 years can be proposed; this would be of the order of 1 to 2 per 100,000 women-years. In other words, one to two women per 10,000 with a breast implant over a period of ten years could develop BIA-ALCL, provided that all the assumptions, which are still difficult to assess at this time, are valid.

The number of cases is too low to formally identify other risk factors associated with the occurrence of this disease, than the presence of a breast implant.

The published data are subject to many biases. Furthermore, there are many missing data, both from the literature and from the French cases. Nevertheless, given the data presented, the group of experts judges that it is necessary to explore the potential association between macrotexturing of the implant and the occurrence of BIA-ALCL.

In light of these data, it is not recommended that preventive explantation be offered to women with a breast implant, regardless of type, because of the risk of BIA-ALCL.

MANAGEMENT OF WOMEN WITH BREAST IMPLANTS WHO ARE SUSPECTED OF HAVING BIA-ALCL

Where there are functional or physical signs (effusion, swelling, pain, inflammation, mass, ulceration, change in general condition), particularly far of the post-operative time in a woman with a breast implant, the diagnosis of BIA-ALCL should be considered. It is recommended that an ultrasound be carried out as a first-line test for effusion around the implant, a mass, or capsular thickening, and to explore the lymph nodes. If this examination is not helpful, an MRI is recommended as a second-line test.

Diagnosis of BIA-ALCL is established by the pathologist and following a confirmatory anatomopathological examination by the LYMPHOPATH national network of experts.

If an effusion is seen on imaging, fine needle aspiration should be carried out. When a mass and/or satellite adenopathy is discovered, specimens are required for cytology and histology (biopsy, fine needle aspiration).

Cytological analysis of fine needle aspirate and anatomopathological analysis of the biopsy are required. An immunophenotypic and molecular study should always complete the morphological analysis of liquid or tissue specimens.

In the event of a capsulectomy (removal of the capsule) or capsulotomy (opening of the capsule), any suspicious lesions (particularly where there are signs of inflammation) or any effusion should be analysed by the pathologist.

In the event of an anatomopathological lymphoma diagnosis or where there is any doubt, the specimen should be sent to the LYMPHOPATH network for a confirmatory examination as a matter of routine.

MANAGEMENT OF WOMEN WITH BIA-ALCL DIAGNOSIS

Following confirmation of the anatomopathological diagnosis by confirmatory examination via the LYMPHOPATH network, the patient should be referred to a haematologist who will assess the extent of the lymphoma.

As part of medical device vigilance, it is compulsory for health professionals to notify ANSM of the occurrence of a case of BIA-ALCL.

The course of action should be discussed at a “Multidisciplinary Consultative Meeting”. The establishment of a national “Multidisciplinary Consultative Meeting” specialising in the care of BIA-ALCL is recommended by the expert group.

Regardless of the extent of disease at diagnosis, a complete capsulectomy should be carried out, in an authorised centre for the surgical treatment of cancers. Where appropriate, a contralateral explantation is performed, and it is recommended that a specimen be submitted for anatomopathological testing. Reimplantation cannot be recommended, given the current knowledge

on the origin and development of this disease. Any decision to reimplant should be discussed at the Multidisciplinary Consultative Meeting on a case by case basis.

Where the disease is localised and it has been possible to perform a complete capsulectomy, surveillance by the haematologist and surgeon is recommended. By analogy with other indolent lymphomas, this surveillance can be carried out at 4-month intervals for the first 2 years.

When the disease is extensive (stage II-IV), or when it has not been possible to perform a complete capsulectomy, treatment in addition to surgery (chemotherapy/radiotherapy) should be discussed at a Multidisciplinary Consultative Meeting.

The group of experts recommends the establishment of a clinical registry of BIA-ALCL cases, in association with the specialised national Multidisciplinary Consultative Meeting and the LYMPHOPATH network.

MONITORING AND INFORMING WOMEN WITH BREAST IMPLANTS REGARDING THE RISK OF BIA-ALCL

For women with breast implants who are free of clinical breast signs, the expert group does not recommend particular monitoring beyond what currently exists for all women. It is recalled that all women should have a clinical breast examination annually from the age of 25 years, and that women eligible for the organised breast cancer screening and women with an increased risk of breast cancer are also monitored by specific imaging (French National Authority for Health [HAS], 2014).

The health professionals responsible for this monitoring (general practitioners, surgeons, oncologists, gynaecologists, radiologists, midwives, etc.) should be informed and made aware of the local signs that can be associated with the occurrence of BIA-ALCL.

Information on the risk of BIA-ALCL should be incorporated into an information sheet given to women prior to the insertion of a breast implant. Information on the clinical signs that should prompt women to seek medical advice should be included.

Any women having a breast implant inserted should be given a card that lists the features of the implant.

APPENDIX 1: Care algorithm for breast implant-associated ALCL



